Cell Metabolism
Previews

Autonomic MC Sets the Metabolic Tone

Chun-Xia Yi,[1] Andries Kalsbeek,[2] and Matthias H. Tschöp[1,*]
[1]Metabolic Disease Institute, Div. of Endocrinology, Department of Medicine, University of Cincinnati, Cincinnati, OH 45226, USA
[2]Department of Endocrinology and Metabolism, Academic Medical Center (AMC), Meibergdreef 15, 1105 AZ and Hypothalamic Integration Mechanisms, Netherlands Institute for Neuroscience, Meibergdreef 47, 1105 BA Amsterdam, The Netherlands
*Correspondence: tschoemh@ucmail.uc.edu
DOI 10.1016/j.cmet.2011.01.014

The CNS melanocortin (MC) and the autonomic nervous (ANS) system represent key regulators of energy homeostasis. In this issue, Rossi et al. (2011) dissect metabolic functions of MC4 receptors based on anatomic localization within the ANS by re-expressing MC4R subpopulations in cholinergic or brainstem neurons of MC4R-KO mice.

In 1848, the French physiologist Claude Bernard envisioned that hepatic glucose production was under the control of autonomic nerves. After showing this in rabbits (Bernard, 1850), numerous studies have confirmed the essential role of the autonomic nervous system (ANS) in glucose, energy, and lipid metabolism. However, our insights into the mechanisms that fine tune the balance between the two main components of the ANS, i.e., its sympathetic and parasympathetic branch, remain poorly understood. In this issue, Rossi et al. (2011) use advanced LoxP-Cre tools to rescue melanocortin (MC) signaling in distinct subpopulations of ANS motor neurons in melanocortin 4 receptor null (MC4R-KO) mice (Figure 1). Their advanced genetic dissection studies elegantly reveal how the preganglionic sympathetic and parasympathetic neurons are under direct control by the MC system and exert well-defined differential roles in the central control of energy and glucose metabolism.

MC signaling plays an important role in energy metabolism, as clearly evidenced by the fact that MC4R deficiency represents the commonest known monogenic cause of human obesity. Rossi and colleagues used loxP-modified null Mc4r alleles (loxTB MC4R) to genetically dissect the specific role of MC signaling in sympathetic versus parasympathetic preganglionic neurons. This was achieved by either the general re-expression of MC4R in all cholinergic neurons including brainstem and spinal cord autonomic motorneurons (loxTB MC4R, ChAT-Cre), or by specifically re-expressing MC4Rs only in autonomic control neurons, including the parasympathetic motor neurons in the dorsal motor nucleus of the vagus (loxTB MC4R and Phox2b-Cre), but excluding the sympathetic motorneurons in the spinal cord. Due to the lack of suitably specific sympathetic or spinal cord neuronal Cre mouse models, the phenotype of MC4R re-expression in only sympathetic motor neurons of MC4R null mice was indirectly deduced by comparing and "subtracting" the metabolic phenotypes of the general and brainstem MC4R rescue models. Re-expression of MC4R in cholinergic neurons resulted in a 10% decrease of body weight, lowered adiposity, and a significant increase of energy expenditure in comparison to loxTB MC4R mice, which exhibited a phenotype identical to global MC4R null mice. Comparable changes were not observed when MC signaling was reconstituted in the autonomic brainstem neurons only. The authors therefore concluded that the lowered body weight and elevated energy expenditure resulted from re-expression in sympathetic motor neurons. Interestingly, reactivation of MC4R signaling in cholinergic neurons also improved hyperinsulinemia and hyperglycemia, while re-expression of MC4R selectively in brainstem neurons only improved hyperinsulinemia. Specifically, they found improved efficiency of insulin-induced inhibition of hepatic glucose production following general re-expression of MC4R in cholinergic neurons, but not with specific re-expression in the vagal motor neurons. These observations nicely fit with previous data (van den Hoek et al., 2008), and indicate that the activity of the sympathetic input to the liver is balanced by the NPY- and POMC-containing projections from the arcuate nucleus. An increased NPY input to sympathetic preautonomic hypothalamic neurons reduces hepatic insulin sensitivity, whereas a reinstatement of MC signaling (derived from the arcuate nucleus) onto sympathetic preganglionic neurons in the spinal cord increases hepatic insulin sensitivity (Rossi et al., 2011).

The current study clarifies the important role of the MC4R as a modulator of the ANS and thereby of energy expenditure and glucose homeostasis. Previous studies of the same team using reactivation of MC4Rs in the PVN and part of the amygdala showed a clear rescue of the hyperphagia in MC4R null mice (Balthasar et al., 2005). Together, these studies reveal a highly differentiated manner in which the MC4R contributes to energy metabolism. This alerts us that when considering therapeutics, we should not concentrate on one hormone, peptide, receptor, and so on, but also take into account their specific targets—i.e., the anatomical location. A major future challenge is whether it is possible to further restrict MC4R expression to subpopulations of neurons connected to specific organs or tissues, or from the point of pharmacological intervention, whether it is possible to stimulate energy expenditure and insulin sensitivity, without causing side effects on heart rate and blood pressure.

As with any scientific approach, there are pitfalls and shortcomings. For example, the knock-in of a targeted gene in a specific cell population using the Cre-lox system is only as specific as the promoter used and only meaningful if the Cre mouse is specific for, completely expressed in, and limited to, all of those target cells. As with all nonconditional models, compensatory changes during

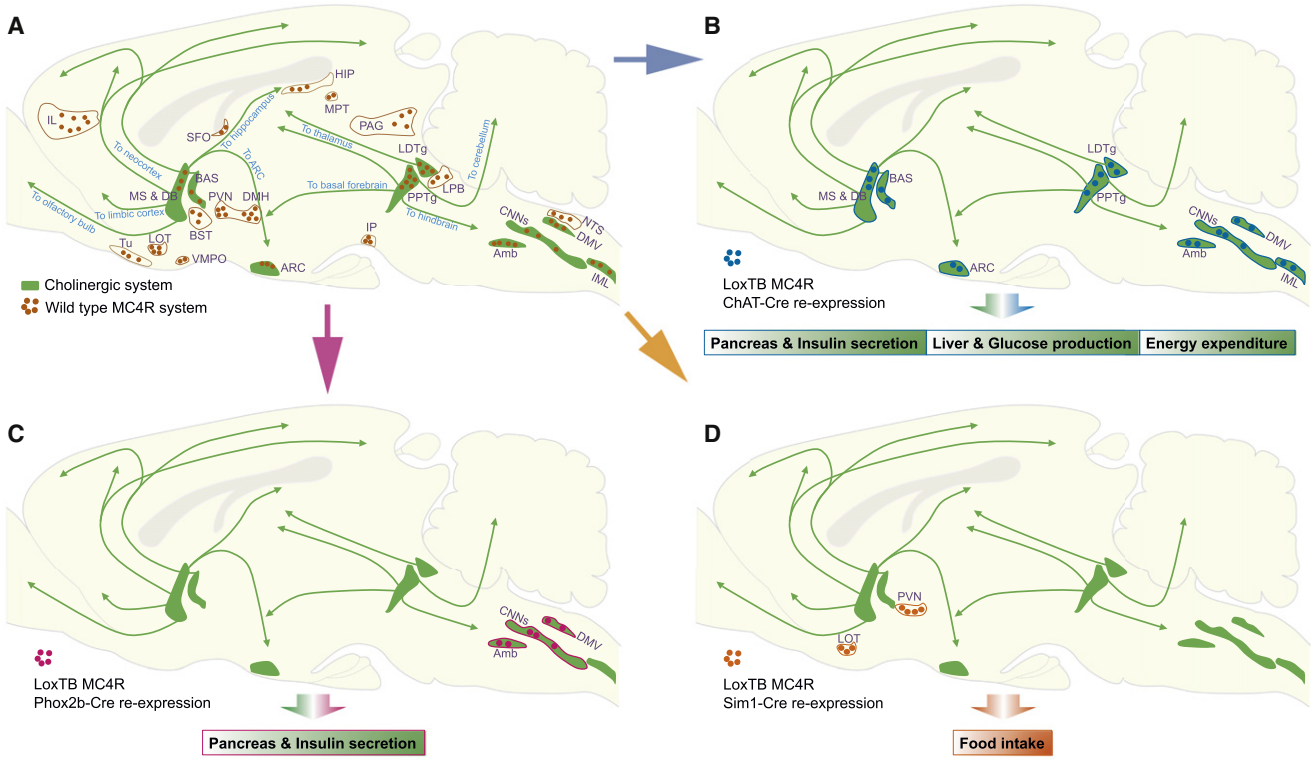

Figure 1. Genetic Dissection of CNS Metabolic Control: Functional Neuroanatomy Linking Cholinergic and Melanocortin Systems
(A–D) Both the cholinergic (Woolf, 1991) and MC4R system (Liu et al., 2003) are globally distributed from forebrain to hindbrain (A). In the study of Rossi et al., MC4R is re-expressed either in all cholinergic neurons (B), or specifically re-expressed in brainstem autonomic control neurons (C). In the study of Balthasar et al., MC4R was re-expressed in noncholinergic neurons in the hypothalamic paraventricular nuclei (PVN) and the amygdala in limbic cortex (D). Reinstatement of MC4R signaling in PVN and amygdala mainly affected feeding behavior, reinstatement of MC4R in parasympathetic preganglionic neurons is probably responsible for the control of circulating insulin level, and reinstatement of MC4R in preganglionic sympathetic neurons is most likely involved in the regulation of hepatic insulin sentivity and energy expenditure. Amb: nucleus ambiguous; BAS: nuclei basalis and ventral globus pallidus; BST: bed nucleus of the stria terminalis; CNNs: cranial nerves nuclei; DMH: dorsomedial hypothalamus; HIP: hippocampus; IL: infralimbic cortex; IML: intermediolateral column; IP: interpeduncular nucleus, LDT: laterodorsal tegmental; LOT: nucleus of the lateral olfactory tract; LPB: lateral parabrachial nuclei; MPT: medial pretectal nucleus; MS and DB: medial septal nucleus and diagonal band; NTS: nucleus of solitary tract; PAG: periaqueductal gray; PPT: pedunculopontine tegmental; SFO: subfornical organ; Tu: olfactory tubercle; VMPO: ventromedial preoptic area.

development cannot be excluded. For the current study, it is unclear, in the general knockin, what the contribution is of the re-expression of MC4R in the acetylcholine containing neurons in the arcuate, the laterodorsal tegmental (LDT), and the pedunculopontine tegmental (PPT) nucleus to the phenotype observed.

How do the current findings of an important role for sympathetic activity in the control of hepatic glucose production relate to the findings of Pocai et al. (2005) that claim a key role for vagal activity in the control of hepatic glucose production? Where are the melanocortins that affect the MC4R on the preganglionic neurons in the brainstem and spinal cord coming from? What is the significance of the ectopic expression of MC4R in the forebrain acetylcholine neurons that provide such a massive input to the cortex? Additional questions relate to the specificity of the currently observed effects on glucose metabolism as well. MC4R-KO mice display hepatic steatosis, whereas activation of the MC system reduces the expression of lipogenic genes in the liver. Recently, it was discovered that the CNS MC system directly controls circulating HDL cholesterol (Perez-Tilve et al., 2010) and triglyceride metabolism in liver and adipose tissue (Nogueiras et al., 2007). Identification of the responsible MC4R subpopulation would be important and might allow for development of more specific therapeutics.

In conclusion, the story of which Claude Bernard started and which Rossi and colleagues so elegantly continued is far from over. We now know that hepatocytes respond to MC signaling in the autonomic nervous system. But in order to develop a sound treatment for the metabolic disease epidemic we are facing today, we need to find a way to orchestrate all tissues to receive their tailored balance of sympathetic and parasympathetic tones.

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Adiponectin Receptor Signaling: A New Layer to the Current Model

Takashi Kadowaki[1,*] and Toshimasa Yamauchi[1]
[1]Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
*Correspondence: kadowaki-3im@h.u-tokyo.ac.jp
DOI 10.1016/j.cmet.2011.01.012

Adiponectin and its receptors, AdipoR1 and AdipoR2, regulate glucose and fatty acid metabolism partly via activation of AMP-activated protein kinase (AMPK). Recent work in *Nature Medicine* (Holland et al., 2011) suggests that adiponectin stimulates ceramidase activity through AdipoR1 and AdipoR2, an activity potentially involved in promoting cell survival.

Adiponectin is a major insulin-sensitizing adipokine (Berg et al., 2001; Fruebis et al., 2001; Yamauchi et al., 2001). Adiponectin levels are decreased in cases of obesity and type 2 diabetes, a finding that has attracted enormous interest in the scientific community. Adiponectin stimulates AMP-activated protein kinase (AMPK), and this action has been implicated in its insulin-sensitizing function in liver and muscle (Yamauchi et al., 2002; Nawrocki et al., 2006). Both adiponectin receptors, AdipoR1 and AdipoR2 (Yamauchi et al., 2003), mediate the major part of the insulin-sensitizing action of adiponectin in liver, while AdipoR1 primarily does so in muscle (Yamauchi et al., 2007; Iwabu et al., 2010). Although it was previously shown that AdipoR1 and AdipoR2 regulate glucose and fatty acid metabolism partly via activation of AMPK, Ca^{2+}, and PPARα signaling pathways, it was not known whether these signaling pathways are sufficient to explain the pleiotropic actions of adiponectin. This study adds ceramide signaling as a new pathway involved in mediating such pleiotropic effects.

Scherer and colleagues also confirm that adiponectin ameliorates insulin resistance induced by a high-fat diet (HFD) in an AdipoR1- or AdipoR2-dependent fashion (Holland et al., 2011). Interestingly, they demonstrate that adiponectin lowers cellular ceramide levels via activation of ceramidase, which converts ceramide to sphingosine, an effect that appears to be dependent on activation of AdipoR1 or AdipoR2. They found that in liver, overexpression of adiponectin, AdipoR1, or AdipoR2 reduces hepatic ceramide levels and improves insulin sensitivity, while deficiency of adiponectin increases hepatic ceramide levels and exacerbates insulin resistance. Because increased ceramide levels correlate with impaired insulin action in muscle (Savage et al., 2007), it is tempting to speculate that the relationship between adiponectin-induced changes in ceramide levels and those in insulin sensitivity may be causal; this hypothesis should be examined experimentally.

Accumulation of ceramide has also been implicated in both β cell decompensation and heart failure induced by a HFD. This may be due to reduced ceramidase activity associated with reduced sphingosine, leading to reduced sphingosine 1-phosphate (S1P), a potent inhibitor of apoptosis generated via phosphorylation of sphingosine by sphingosine kinase. Scherer and colleagues use their elegant model of conditionally induced apoptosis to demonstrate that adiponectin both increases S1P and protects from apoptotic cell death induced by either palmitate or C2-ceramide in cardiac myocytes and pancreatic β cells (Holland et al., 2011). Because this protection is reversed by either an inhibitor of ceramide biosynthesis or S1P itself, it seems likely that adiponectin-induced S1P generation protects cardiac myocytes and β cells from cell death.

In this study, adiponectin significantly reduced hepatic ceramide levels and blood glucose levels in mice deficient in LKB1, an upstream activator of AMPK, which had increased basal hepatic ceramide levels and blood glucose levels compared to controls (Holland et al., 2011). From these data, they argue that adiponectin reduces hepatic ceramide levels independent of AMPK. No evidence yet exists to support this claim, as it may be difficult to draw a conclusion on the role of AMPK per se in decreasing glucose levels or on the role of adiponectin on lowering ceramide in this system. Moreover, the activation of AMPK and Ca^{2+} signaling pathways occurs within minutes after adiponectin stimulation, whereas activation of ceramidase appears to occur within a half hour, raising some question of whether ceramidase is the most upstream event following AdipoR1 or AdipoR2 activation.